IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Howard Bernstein, Donald Chickering, Sarwat Khattak, and Julie Straub

Serial No.: 09/731,412 Art Unit: 1617

Filed: December 6, 2000 Examiner: E.J. Webman

For: *MATRICES FORMED OF POLYMER AND HYDROPHOBIC COMPOUNDS FOR USE IN DRUG DELIVERY*

Assistant Commissioner for Patents
Washington, D.C. 20231

APPEAL BRIEF

Sir:

This is an appeal from the final rejection of claims 20-24, and 27-32 in the Office Action mailed June 21, 2002, in the above-identified patent application. A Notice of Appeal was mailed on June 27, 2002. A Petition for an extension of Time for one month and the appropriate fee for a small entity, and a check in the amount of $160.00 for the filing of this Appeal Brief for a small entity are also enclosed. It is believed that no additional fee is required with this submission. However, should an additional fee be required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 50-1868.

(1) REAL PARTY IN INTEREST

The real party in interest of this application is the assignee Acusphere, Inc., Cambridge, Massachusetts.

(2) RELATED APPEALS AND INTERFERENCES

There is one related appeal known to appellant, the undersigned, or appellant's assignee which directly affects, which would be directly affected by, or which would have a bearing on the Board's decision in this appeal, the appeal of the final rejection of the claims in the divisional patent application, U.S.S.N. 09/730,694 filed December 6, 2000.

(3) STATUS OF CLAIMS ON APPEAL

Claims 20-24 and 27-32 are pending. Claims 20-24 and 27-32 are on appeal. Claims 25, 26, 33 and 34 are objected to. The text of each claim on appeal, as pending, is set forth in an Appendix to this Appeal Brief.

(4) STATUS OF AMENDMENTS

The claims were last amended in the Amendment mailed February 22, 2002. In the Advisory Action mailed June 21, 2002, the Examiner indicated that the amendment mailed June 6, 2002, would not be entered.

(5) SUMMARY OF THE INVENTION

The claims are directed to a method for administering a therapeutic or prophylactic agent comprising administering to a patient a matrix for delivery of a therapeutic or prophylactic agent (claim 20 as originally filed; page 4, line 13-15) wherein the matrix is formed of a biocompatible polymer having incorporated therein an therapeutic or prophylactic agent and an effective amount of a hydrophobic or amphiphilic compound to modify the diffusion of water into the matrix and the release of the therapeutic or prophylactic agent from the matrix, wherein the drug is released over shorter periods of time as compared to release from matrices not incorporating

the hydrophobic or amphiphilic compound (claims 1, 8 as originally filed; page 4, lines 18-23; page 11, line 18). The matrix is formed by emulsifying a polymer solution, the therapeutic or prophylactic agent, a hydrophobic or amphiphilic compound, and pore forming agent, then removing solvent and pore forming agent to produce a porous matrix of polymer, therapeutic or prophylactic agent and hydrophobic or amphiphilic compound (page 8 lines 1-3; page 16, lines 5-8) in the form of microparticles (claim 2 as originally filed; page 4, line 29). The hydrophobic or amphiphilic compound is typically incorporated into the matrix at a ratio of between 0.01 and 60 by weight of hydrophobic compound to weight of polymer (claim 3 as originally filed; page 10, line 12). If the hydrophobic or amphiphilic compound is a lipid, then it is typically incorporated into the matrix at a ratio of between 0.01 and 30 (weight lipid/weight matrix material) (claim 4 as originally filed; page 10, line 13). The lipid can be fatty acids or derivatives thereof, mono-, di or triglycerides, phospholipids, sphingolipids, cholesterol, steroid derivatives, oils, vitamins or terpenes (claim 5 as originally filed; page 8,lines 11-14; page 10, lines 1-2). The material can then be administered topically to a mucosal surface, to the pulmonary system, or by injection (page 16, line 11 to page 17, line 15; claims 31-34).

(6) ISSUES ON APPEAL

The issue presented on appeal is:

(1) whether claims 20-24 and 27-32 lack novelty under 35 U.S.C. § 102(e) over U.S. Patent No. 5,942,253 to Gombotz *et al.* ("Gombotz").

(7) GROUPING OF CLAIMS

The claims do not stand or fall together, as discussed below.

(8) ARGUMENTS

(a) The Claimed Invention

The encapsulation of drugs in polymers for delivery to a patient frequently results in too slow a release of the drug following an initial burst of drug release. It is highly desirable to increase the rate of release following the initial burst.

The claimed invention is a method for administering a matrix for delivery of a therapeutic or prophylactic agent. The matrix is defined by its method of manufacture and its drug release properties. The drug is released over shorter time periods from the matrix, in comparison to the same matrix not incorporating a hydrophobic or amphiphilic compound and not made with a pore forming agent. The method and reagents for making the matrix result in the formation of matrix having greatly enhanced release properties following administration of the matrix. An important step in the method is that the drug to be released and hydrophobic/amphiphilic compound must be dissolved with the polymer or dispersed as a solid or a liquid in the polymer solution prior to forming the matrix, along with the pore forming agent. The matrix is formed by emulsifying a polymer solution, the therapeutic or prophylactic agent, hydrophobic or amphiphilic agent compound, and pore forming agent, then removing solvent and pore forming agent to produce the matrix. The matrix then releases the therapeutic or prophylactic agent faster due to the increased porosity (surface area) of the matrix which results from the use of the pore forming agents, as well as the inclusion of the hydrophobic or amphiphilic compound. This is

counterintuitive since one typically thinks of hydrophobic compounds as repelling water, not increasing the rate of dispersion of drug within the aqueous environment of the body. The high degree of porosity greatly increases the diffusion of water into the matrix and the release of the therapeutic or prophylactic agent, even when the drug is very hydrophobic, from the matrix.

The method of making the matrix to be administered can be summarized as follows:

Adding (1) hydrophobic or amphiphilic compound, (2) the therapeutic or prophylactic agent to be incorporated, and (3) a pore forming agent;

Emulsifying these materials;

Removing solvent and pore forming agent to form a porous matrix.

The pore forming agent is critical to producing a matrix having the desired release properties. The Board's attention is drawn to the Declaration under 37 C.F.R. 1.132 of Dr. Bernstein, filed with the amendment mailed February 22, 2002, comparing the release kinetics of matrices differing solely by whether or not a pore forming agent was including in the manufacturing process. The figure shows that significantly greater release was obtained in the two hours in which release was measured for the materials made with a pore forming agent.

(b) Rejections Under 35 U.S.C. § 102

1. The Legal Standard under 35 U.S.C. 102

Anticipation requires the disclosure, in a single prior art reference, of every element of the claim. Hybritech, Inc. v. Monoclonal Antibodies, Inc., 231 USPQ 81, 90 (Fed. Cir. 1986). Absence of a claimed element from a prior art reference negates anticipation. Atlas Powder Co. v. E.I. du Pont de Nemours & Co., 750 F.2d 1569,224 USPQ 409 (Fed. Cir. 1984).

A reference can be shown not to inherently disclose an element if it can be demonstrated that the combination results in different properties.

> "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.'" In re Robertson, 169 F.3d 743,745,49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999)

2. Gombotz does not anticipate the method of claim 20.

Claims 20-24 and 27-32 were rejected under 35 U.S.C. § 102(e) as disclosed by U.S. Patent No. 5,942,253 to Gombotz *et al.* ("Gombotz"). The basis for the rejection is that Gombotz teaches injection or transmucosal delivery of microparticles including polylactic acid (a hydrophobic polymer) or a biadhesive polymer (abstract). Drug is present in a range of from 0.1%-10%. Lipid, a hydrophobic agent, in a ratio of 4:1 lipid to drug, is disclosed.

The claimed method defines the material to be administered in terms of its release properties and in terms of its method of manufacture.

In terms of the method of manufacture, appellants' claim a material produced by a method that requires incorporation of a pore forming agent, and then removal of the pore forming agent with the solvent in which the polymer is dissolved, to form a porous matrix. Gombotz does not disclose this feature. Microsphere preparation is described in Gombotz

beginning at col. 7, line 46, "Microsphere Preparation". As noted at col. 8, lines 15-16, polymer is dissolved in solvent and drug (GM-CSF) is added with stirring (col. 8, lines 18-20). The solvent is then evaporated, and the resulting microspheres washed with water and dried (col. 8, lines 21-24). Conspicuously absent is any mention of a pore forming agent, yet this is critical to appellants' method. Also missing is any reference to including a hydrophobic or amphiphilic compound.

Pore forming agents are referred to at col. 9, lines 52-54. These are described as water soluble compounds such as inorganic salts and sugars in the form of particles. There is no disclosure of any specific step to remove the pore forming agents, and since they are water soluble, they would not inherently be removed with a non-aqueous polymer solvent. Presumably the water soluble particles would be removed, at least in part, when the polymer solution is exposed to water or when the already formed microspheres are washed with water. There is no disclosure of a volatile pore forming agent.

"Stabilizers" are referenced at col. 9, line 64, to col. 10, line 8. Some of these are described as lipids or surfactants. However, it appears these are added to the drug to be released, not to the polymer, and to stabilize the drug, not alter release properties of the matrix.

Therefore Gombotz does not disclose adding either a pore forming material that is removed with the polymer solvent to form a porous matrix, nor a hydrophobic compound incorporated into the matrix (as opposed to the therapeutic compound).

Since Gombotz does not disclose each claimed step, and in particular removal of the pore forming agent with the solvent, to yield a porous matrix, Gombotz does not anticipate claim 20.

Gombotz also does not anticipate the claimed method since there is no disclosure of a matrix which is produced with a pore forming agent removed prior to matrix formation and which incorporates a hydrophobic or amphiphilic compound, both of which result in modified release of drug. Gombotz refers to the hydrophobic or amphiphilic compounds only with respect to "degradation" of the polymer (col. 9, lines 37-50) and "stabilization" (col. 9, line 64 to col. 10, line 8), not with respect to release.

As demonstrated by Dr. Bernstein's declaration, the inclusion of the hydrophobic or amphiphilic compound (compare (1) on page 7 with (2) on page 8) is significant at 120 minutes. This is surprising since one would have thought inclusion of a material that repels water would decrease release into an aqueous environment. The results are even more striking when one adds a pore forming agent removed with the polymer solvent ((3) on page 8, black diamonds in figure).

Gombotz also does not anticipate the dependent claims

Claims 21 and 22 define the concentration of the hydrophobic or amphiphilic compound. The ratios in Gombotz at col. 10, lines 5-8, are not a ratio of hydrophobic compound to polymer ratio, but compound to protein, i.e., therapeutic agent, since it is the therapeutic agent which the compound is intended to stabilize.

Gombotz does not anticipate claims 31, 33, and 34

Claims 33 and 34 are drawn to a method of formulating the matrix containing therapeutic agent for administration rectally or vaginally, or for pulmonary administration. Gombotz does

not teach formulating for delivery other than by injection or topically to the skin or mucosa (col 10, lines 11-20 and 58-67).

Gombotz does not inherently disclose the claimed method

There is no reference to variation of the protocol in Gombotz and the mere possibility does not confer inherency. Gombotz teaches the addition of water soluble particulate pore formers that are presumably removed only in part (at most) when polymer solution is emulsified with a water phase or after the matrix is formed by washing with water, not during the formation of the microparticles. The matrices which would result from each of these methods are different. Gombotz does not disclose adding hydrophobic or amphiphilic compound to the polymer solution, but to stabilize the therapeutic. This would not result in the same distribution of hydrophobic or amphiphilic compound within the matrix, with the result that the release properties would be different.

"In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." Ex parte Levy, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990)

It is also necessary to establish inherency, that the properties in the subject matter be both inherent *and* disclosed in the specification. "we look not only to the subject matter which is literally recited in the claim in question.... But also to those properties of the subject matter which are inherent in the subject matter *and* are disclosed in the specification... Just as we look to a chemical and its properties when we examine the obviousness of a composition of matter

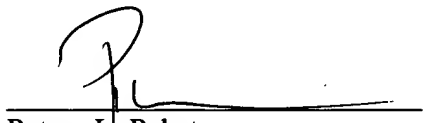
claim, it is this invention *as a whole*, and not some part of it, which must be made obvious under 35 USC 103." In re Antonie, 559 F.2d 618, 620, 195 USPQ 6,8 (CCPA 1977)

This standard has not been met here. Gombotz neither explicitly nor inherently discloses the claimed method because the materials to be administered are distinct, based upon composition and method of manufacture.

(9) SUMMARY AND CONCLUSION

Claims 20-34 are not disclosed explicitly nor inherently under 35 U.S.C. 102(e) over Gombotz.

Respectfully submitted,



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I hereby certify that this paper, along with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Jean Hicks

Jean Hicks

Date: September 6, 2002

Appendix: Claims On Appeal

20. (twice amended) A method for administering a therapeutic or prophylactic agent comprising administering to a patient a matrix for delivery of a therapeutic or prophylactic agent,

wherein the matrix is formed of a biocompatible polymer having incorporated therein an therapeutic or prophylactic agent and an effective amount of a hydrophobic or amphiphilic compound to modify the diffusion of water into the matrix and the release of the therapeutic or prophylactic agent from the matrix, wherein the drug is released over shorter periods of time as compared to release from matrices not incorporating the hydrophobic or amphiphilic compound,

the matrix being formed by a method comprising emulsifying a polymer solution, the therapeutic or prophylactic agent, hydrophobic or amphiphilic compound, and pore forming agent, then removing solvent and pore forming agent to produce a matrix.

21. The method of claim 20 wherein the matrix is in the form of microparticles.

22. The method of claim 20 wherein the hydrophobic or amphiphilic compound is incorporated into the matrix at a ratio of between 0.01 and 60 by weight of hydrophobic compound to weight of polymer.

23. The method of claim 20 wherein the hydrophobic or amphiphilic compound is a lipid incorporated into the matrix at a ratio of between 0.01 and 30 (weight lipid/weight matrix material).

24. The method of claim 23 wherein the lipid is selected from the group consisting of fatty acids and derivatives, mono-, di and triglycerides, phospholipids, sphingolipids, cholesterol and steroid derivatives, oils, vitamins and terpenes.

25. The method of claim 24 wherein the lipid is a phospholipid selected from the group consisting of phosphatidic acids, phosphatidyl cholines with both saturated and unsaturated lipids, phosphatidyl ethanolamines, phosphatidylglycerols, phosphatidylserines, phosphatidylinositols, lysophosphatidyl derivatives, cardiolipin, and β-acyl-y-alkyl phospholipids.

26. The method of claim 25 wherein the phospholipid is selected from the group consisting of dioleoylphosphatidylcholine, dimyristoylphosphatidylcholine, dipentadecanoylphosphatidylcholine dilauroylphosphatidylcholine, dipalmitoylphosphatidylcholine, distearoylphosphatidylcholine, diarachidoylphosphatidylcholine, dibehenoylphosphatidylcholine, ditricosanoylphosphatidylcholine, dilignoceroylphatidylcholine; and phosphatidylethanolamines.

27. The method of claim 20 wherein the agent is a therapeutic agent.

28. The method of claim 20 wherein the matrix is formed of a bioadhesive polymer.

29. The method of claim 20 wherein the matrix is formed of a polymer selected from the group consisting of poly(hydroxy acids), polyanhydrides, polyorthoesters, polyamides, polycarbonates, polyalkylenes, polyalkylene glycols, polyalkylene oxides, polyalkylene terepthalates, polyvinyl alcohols, polyvinyl ethers, polyvinyl esters, polyvinyl halides, polyvinylpyrrolidone, polysiloxanes, poly(vinyl alcohols), poly(vinyl acetate), polystyrene, polyurethanes and co-polymers thereof, synthetic celluloses, polyacrylic acids, poly(butyric acid), poly(valeric acid), and poly(lactide-co-caprolactone), ethylene vinyl acetate, copolymers and blends thereof.

30. The method of claim 20 wherein the matrix is formed of a protein or polysaccharide.

31. The method of claim 20 wherein the matrix is in a pharmaceutically acceptable carrier for topical application or application to a mucosal surface.

32. The method of claim 20 wherein the matrix is in a pharmaceutically acceptable carrier for injection.

33. The method of claim 20 wherein the matrix is formulated for administration rectally or vaginally.

34. The method of claim 21 wherein the microparticles are formulated for pulmonary administration.

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